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**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the application of: Patrick T. PRENDERGAST and Paul ARMSTRONG

Ser. No.: 10/612,476

Group Art Unit: Not assigned

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Examiner: Not assigned

Conf. No.: 7731

For: DITHIOLTHIONE COMPOUNDS FOR THE TREATMENT OF  
NEUROLOGICAL DISORDERS AND FOR MEMORY ENHANCEMENT

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

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Janet M. Stevens

**SUBMISSION OF CERTIFIED COPIES OF PRIORITY DOCUMENTS**

Sir:

The benefit of the filing dates of the following prior foreign applications filed in the following foreign country was requested by applicants on July 2, 2003 for the above-identified application:

<u>Country</u>	<u>Application Number</u>	<u>Filing Date</u>
IRELAND	2000/0302	April 13, 2000
IRELAND	2000/0304	April 13, 2000

In support of this claim, certified copies of the Irish Applications are enclosed herewith.

Respectfully submitted,

Kevin C. Brown  
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November 14, 2003

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I HEREBY CERTIFY that annexed hereto is a true copy of documents filed in connection with the following patent application:

Application No. 2000/0302

Date of Filing 13 April 2000

Applicant PATRICK T. PRENDERGAST, an Irish citizen, of Baybush, Straffan, Co Kildare

Dated this 30 day of October 2003.



An officer authorised by the  
Controller of Patents, Designs and Trademarks.

## REQUEST FOR THE GRANT OF A PATENT

PATENTS ACT, 1992

The Applicant(s) named herein hereby request(s)  
☒ the grant of a patent under Part II of the Act

☐ the grant of a short-term patent under Part III of  
the Act  
on the basis of the information furnished hereunder.

1. Applicant(s)

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Description/Nationality

IRISH

2. Title of Invention

DITHIOLTHIONE COMPOUNDS FOR THE TREATMENT OF  
NEUROLOGICAL DISORDERS AND MEMORY ENHANCEMENT

3. Declaration of Priority on basis of previously filed  
application(s) for same invention (Sections 25 & 26)

Previous filing date

July 29, 1999

Country in or for  
which filed

U.S.

Filing No.

60/145,964

4. Identification of Inventor(s)

Name(s) of person(s) believed  
by Applicant(s) to be the inventor(s) PATRICK T. PRENDERGAST

Address BAYBUSH, STRAFFAN, CO. KILDARE

5. Statement of right to be granted a patent (Section 17 (2) (b) )

6. Items accompanying this Request - tick as appropriate

- (i) ☒ Prescribed filing fee (£ 100 )
- (ii) ☒ Specification containing a description and claims  
☐ Specification containing a description only  
☐ Drawings referred to in description or claims
- (iii) ☒ An abstract
- (iv) ☒ Copy of previous application(s) whose priority is claimed
- (v) ☐ Translation of previous application whose priority is claimed
- (vi) ☐ Authorisation of Agent (this may be given at 8 below if this Request is signed by the Applicant(s))

7. Divisional Application(s)

The following information is applicable to the present application which is made under Section 24 -

Earlier Application No: .....

Filing Date: .....

8. Agent

The following is authorised to act as agent in all proceedings connected with the obtaining of a patent to which this request relates and in relation to any patent granted -

Name

Address

9. Address for Service (if different from that at 8)

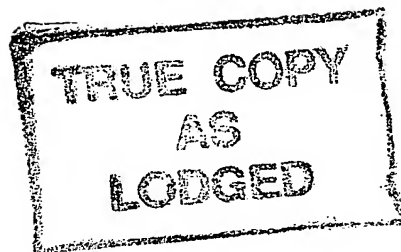
Bay Bds 4  
STRAFFAN  
Co. KILDARE (01-6272636)

Signed

Name(s) :

Capacity (if applicant is a body corporate) :

Date



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APPROVED

**DITHIOLTHIONE COMPOUNDS FOR THE TREATMENT OF NEUROLOGICAL  
DISORDERS AND MEMORY ENHANCEMENT**

**INVENTOR: Patrick T. Prendergast**

## **ABSTRACT**

The present invention relates to therapeutic agents, to pharmaceutical compositions containing them and to their use in the treatment of Parkinson's disease, neurological disorders Alzheimer's disease, dementia, Down's syndrome, cerebral haemorrhage, amyloidosis of the Dutch type, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell, Gerstmann-Straussler syndrome, animal scrapie, Dysthymia, Depressive Disorder, Melancholia. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder and in the treatment of persons to effect future memory enhancement, aluminium overload, reperfusion injury, reducing iron levels in mammals, reducing free metal ion levels in mammals, thalassemia, anemia. This invention additionally comprises administering compound to a mammal as a prophylactic for memory enhancement. Compounds of this invention are identified in the attached embodiments. Specifically two compounds of this invention include oltipraz (CAS Number 64224211), 1,2-dithiole-3-thione and Tritium Anethole. Additionally the administration of inhibitors of the enzyme D-amino acid oxidase to mammals as prophylactic and therapeutic agents for indications as outlined above is disclosed.

## **Background of the Invention**

Alzheimer's disease is a leading cause of dementia in the elderly, affecting 5-10% of the population over the age of 65 years ('A Guide to Understanding Alzheimer's Disease and Related

Disorders, edited by Jorm, New York University Press, New York, 1987). In Alzheimer's disease, the parts of the brain essential for cognitive processes such as memory, attention, language, and reasoning degenerate, robbing victims of much that makes us human, including independence. In some inherited forms of Alzheimer's disease, onset is in middle age, but more commonly, symptoms appear from the mid-60's onward. Alzheimer's disease today affects 4-5 million Americans, with slightly more than half of these people receiving care at home, while the others are in many different health care institutions. The prevalence of Alzheimer's disease and other dementia's doubles every 5 years beyond the age of 65, and recent studies indicate that nearly 50% of all people age 85 and older have symptoms of Alzheimer's disease (1997 Progress Report on Alzheimer's Disease, National Institute on Ageing/National Institute of Health). 13% (33 million people) of the total population of the United States are age 65 and older, and this % will climb to 20% by the year 2025 (1997 Progress Report on Alzheimer's Disease, National Institute on Ageing/National Institute of Health).

Alzheimer's disease also puts a heavy economic burden on society as well. A recent study estimated that the cost of caring for one Alzheimer's disease patient with severe cognitive impairments at home or in a nursing home, is more than \$47,000 per year (A Guide to Understanding Alzheimer's Disease and Related Disorders, edited by Jorm, New York University Press, New York, 1987). For a disease that can span from 2 to 20 years, the overall cost of Alzheimer's disease to families and to society is staggering. The annual economic toll of Alzheimer's disease in the United States in terms of health care expenses and lost wages of both patients and their caregivers is estimated at \$80 to \$100 billion (1997 Progress Report on Alzheimer's Disease, National Institute on Ageing/National Institute of Health).

Progressive Memory loss is the one of the common symptoms of Alzheimer's Disease loss of short-term memory (essential for absorbing information). It can interfere with ability to interact socially and perform ones work. Disorientation becomes more pronounced and extends to places and people. Sense of time becomes distorted. Changes in personality, loss of language skills, poor judgement and planning. Depression is common, because of chemical changes in the brain and understandable psychological reaction to the loss of mental abilities. Loss of interest in previously enjoyable activities.

Early and careful evaluation is very important because many conditions, treatable or reversible, can cause dementia. The early signs are very important to watch out for to enable an early diagnosis.

It is possible that anyone can suffer from forgetfulness at times but an Alzheimer's Patient forgets more often and can not recall names, events, mislay keys, forget where they live, etc.

Evidence of Alzheimer's Disease may first be evident in fine hand movements - illegible handwriting, clumsiness in buttoning clothing. Eventually walking, eating can become obviously effected. Difficulty in washing, shaving cooking and simple everyday tasks will be noticeable.

Persons with Alzheimer's Disease may become withdrawn, irritable, have mood swings. Changes in mood and personality are often the most convincing evidence that something is wrong.

Persons with Alzheimer's Disease can get lost in once familiar places - may not recognise own home or relatives - will have problems with days of the week and time. Disorientation becomes more pronounced as the disease progresses - may insist it's time to go home just after arriving - may complain of not having been fed as soon as meal has ended.



The ability to speak and understand words is gradually effected. Searching for words in sentences that make no sense are common.

Criteria for the diagnosis of probable Alzheimer's Disease have been described and include: (1) the presence of a dementia syndrome with defects in two or more areas of cognition; (2) progressive worsening of memory and other cognitive function over time; (3) a relatively intact level of consciousness (4) age at disease onset at a time between 40 and 90 years of age; and (5) the specific absence of any other systemic or central nervous system process that could account for the progressive cognitive deterioration in the individual.

In addition, the probability of an accurate diagnosis in the living patient is augmented by laboratory examinations (such as VDRL and TPT) and by imaging studies (such as computed tomography and magnetic resonance imaging). Such laboratory examinations and/or imaging studies demonstrate the existence and effects of other causes of dementia (such as subdural hematoma, intracranial tumours, infection and brain infarction) and disclose results which are consistent with but are not themselves diagnostic of Alzheimer's Disease. The best clinical diagnosis available to date is only a presumptive determination based on criteria which are evaluations of cognitive and neurological functions for that patient.

According to US Patent 6,027,896 a method of diagnosing & prognosing Alzheimer's disease is disclosed. This method is based on the fact that senile plaque and congophilic angiopathy are abnormal extracellular structures found in abundance in brain of patients with Alzheimer's disease. The biochemical composition of these structures has been extensively studied to better understand their possible role in the pathogenesis of this dementing disease. The mature senile

plaque is a complex structure, consisting of a central core of amyloid fibrils surrounded by dystrophic neurites, axonal terminals and dendrites, microglia and fibrous astrocytes. The amyloid core of the senile plaque surrounding blood vessels produces a peptide of 39 to 43 amino acids termed the beta.-Amyloid (A.beta.) peptide). A,beta. peptide is found in brain in Alzheimer's disease, Down's syndrome, hereditary cerebral haemorrhage of the Dutch type, and in old age. A.beta. is produced by abnormal proteolytic processing of a larger protein, the amyloid precursor protein (APP).

### **Description**

This invention relates to memory enhancement in patients suffering from illnesses consisting of depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, denile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder , Major Depressive Episode including Chronic Type, Melancholis and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumours (e.g. neuroblastoma), haematological cancers, malaria, renal failure, liver disease, reducing iron levels

in mammals, reducing free iron ion levels in mammals, thalassemia, anaemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis. Additionally this patent envisages treating patients having toxic amounts of metal in the body or in certain body compartments.

This invention provides a process for using an amount of compounds disclosed in the attached embodiments. It is an object of this invention to employ an effective dosage of Oltipraz for substantially enhancing the memory function.

It is an object of the present invention to employ one or more compounds as identified in the attached embodiments for use in prophylactically treating a patient for any form of neuronal or cognitive deficiency.

The present invention relates to methods for reducing iron levels in mammals. In a particular aspect, the present invention relates to methods for reducing free iron ion levels in mammals by administration of compounds identified in the attached claims. The present invention relates to the treatment of hosts suffering from iron overload or non-Iron overload diseases and/or conditions, such as thalassemia, anaemia, hereditary hemochromatosis, hemodialysis, stroke and rheumatoid arthritis. In a further aspect, the present invention relates to compositions and formulations useful in the methods disclosed herein.

Raised iron levels promote the oxidation of catecholamines via quinone intermediates and free radical toxicity. The endogenous opioid may cause suppression of proenkephalin A transcription or influence its post transcriptional regulation, and also affect dopamine and other amine storage in vesicles and postsynaptic effect.

The iron excess, the low scavenging enzyme activities, inhibition of mitochondrial metabolism morphological damage to mitochondria and damage to enkephalinergic pathways in Parkinson's Disease result from mitochondrial DNA damage and proteolysis of non functional cytochromes

translated therefrom, The mitochondrial DNA environment, its damage and lack of a pyrimidine dimer repair system predisposes it to the development of Parkinson's Disease. Plaque and tangle formation in Parkinson's Disease and Alzheimer's Disease resulting therefrom are caused by the release of iron, copper and calcium, which activate metal endopeptidases.

Parkinson's Disease may result from age related DNA damage in mitochondria caused by accumulation of free radicals, xenobiotics, dopamine, quinones, radiation, and age related decline in polyamine levels. Copper is particularly active in promoting xenobiotic induced DNA base damage. Paraquat and polyamines, putrescine and spermidine show reciprocal competitive inhibition of uptake.

A 5000 base pair deletion has been observed in some areas of the brain during ageing and in Parkinsonians (Ikebe S. et al). A single base pair mutation or deletion at any of several sites can cause complex 1 deficiency in mitochondrial myopathy patients (Holt 1. J. et al). The significance of these deletions, though likely rare amongst all Parkinson's disease cases is that random DNA base damage can produce a similar pattern of disease.

Disturbance of cytochrome regulation would lead to the iron and opioid defects. Excessive transcription, excessive translation of a normal mitochondrial transcript or an abnormally sequenced or spliced one, or excessive intramitochondrial proteolysis would serve as a source of raised intramitochondrial iron, raised intracellular iron and an endogenous opioid, cytochrome c.

Metal dependent endopeptidases such as the physiological precursor cleaving peptidases i.e. non-lysosomal proteases, and calpains are activated by free metals in vivo. They can be implicated in the pathological changes of dementias, including beta amyloid and neurofibrillary tangle

formation, and demyelination. The molecules involved in generating Lewy bodies, Hirano bodies, Pick bodies, and granulovacuolar degeneration are not known at the present time. Brain copper levels are highest in locus coeruleus, substantia nigra, putamen and globus pallidum respectively. Brain iron levels are highest in globus pallidum, putamen and substantia nigra respectively. Release of metals at particular subcellular sites is likely a common event in the pathogenesis of Alzheimer's, Parkinsonian, Batten's, Pick's dementias and dialysis aluminium induced encephalopathy. Agents which influence subcellular compartmentation and distribution of copper, iron, nickel and aluminium will offer therapeutic prospects in preventing these pathologies. Enzyme inhibition of pre aspartate proteases may not be therapeutically practicable as these proteases serve physiological functions. Regulation of the peptide precursor cleaving enzyme activities by control of free metal levels is an interesting therapeutic avenue. Their significance in dementia pathogenesis is likely due to the absence of other enzyme classes, capable of cleaving at pre aspartate sites.

High levels of CuZn were demonstrated immunohistochemically in the large pyramidal cells of control and Alzheimer's disease patients brains. The localization of the superoxide dismutase gene on chromosome twenty one and the early occurrence of Alzheimer's Disease in Down's syndrome suggest that superoxide dismutase activity and hydrogen peroxide formation may contribute to Alzheimer's pathogenesis. Also the neurons containing high levels of NADPH diaphorase are relatively spared in neonatal hypoxia and hypoglycemia but are affected in Alzheimer's disease. The increase in platelet membrane fluidity, noted in a subgroup of Alzheimer's disease patients, possibly due to dysregulation of platelet membrane biosynthesis is not associated with a higher erythrocyte level of superoxide dismutase.

Iron is deposited as haemosiderin granules in the cytoplasm, and mitochondria filled with ferritin granules have been observed in the neuronal and glial cells of the ventrolateral thalamus, caudate and lenticular nuclei and substantia nigra of Parkinsonian brains (Earle K. M., Asenjo A. et. al., Riederer P. et. al.), and copper, though not detectable in excess in the brain, does overflow into the cerebrospinal fluid. The level of copper overflow correlates with the clinical severity of Parkinson's Disease and the level of Alzheimer type damage present in the patients (Pall H. S. et al).

Though Parkinsonian syndromes can be induced by other metals such as chronic manganese poisoning which causes Parkinsonian like and psychotic symptoms in miners and hepatolenticular degeneration due to copper disposition in Wilson's Disease, excessive levels of metals other than iron have not been observed in idiopathic or post encephalitic Parkinsonism.

The invention also includes a method for treatment of patients having toxic amounts of metal in the body or in certain body compartments which comprises administration to the patient an amount of one or more compounds as described in the attached embodiments to effect reduction of the toxic levels of metal ions in the body of the patient.

The compounds of this invention are useful in the treatment of aluminium intoxication which is found frequently with renal impaired patients, including renal dialysis where aluminium overload in the blood may lead to dialysis encephalopathy.

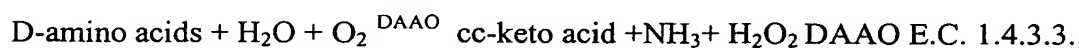
Even though, compounds in this invention may be of value in treating certain animal pathological conditions, they are especially useful to treat a variety of human conditions. Iron overload conditions associated with beta-thalassaemia may be beneficially treated.

In previous studies, it has been discovered that oxidative damage in Alzheimer disease (AD) is confined to neuronal cell bodies, precedes the formation of neuronal pathology, and strongly relates to amyloid- (A $\beta$ ) deposition. This places oxidative damage as the most proximal event reported thus far in the disease process. While many pharmaceutical companies are pursuing the use of “straight antioxidants” it is unlikely that such an approach will significantly ameliorate the progression of the disease especially if used after the onset of clinical symptoms. Indeed, unless sources of free radicals are eliminated from the diseased brain, the use of antioxidants is always going to be of limited pharmacological value. In this regard, there is increasing evidence that iron-centered alterations, likely in conjunction with mitochondrial dysfunction, are central to oxidative damage and neuronal dysfunction in AD. To counteract these abnormalities, metal chelation and metabolic enhancers, either singularly or in combination, are being increasingly viewed as attractive pharmacological agents. Notably, we have shown that Oltipraz [4-methyl-5-(pyrazin-2-yl)-1,2-dithiole-3-thione] is a potent metal chelator that is able to effectively remove redox-active iron from brain sections taken from individuals with Alzheimer disease. Furthermore, and equally importantly from an early therapeutic/preventative angle, Oltipraz is able to significantly attenuate the neurotoxicity of amyloid- $\beta$ , a key pathogenic protein involved in the disease. Again, the mechanisms involved in this neuroprotection revolve around the fact that Oltipraz is able to effectively chelate iron.

The overall result of unchecked oxygen radicals is damage. Importantly, this damage involves all neurons in populations vulnerable to death in AD, not just those containing neurofibrillary tangles.

Reactive oxygen is a ubiquitous by product of both oxidative phosphorylation and the myriad of oxidases necessary to support aerobic metabolism. In AD, in addition to this background level of reactive oxygen, there are a number of additional contributory sources that are thought to play an important role in the disease process: (1) Iron, in a redox-active state, is increased in neurofibrillary tangles as well as in amyloid- deposits. Iron catalyzes the formation of  $\cdot\text{OH}$  from  $\text{H}_2\text{O}_2$  as well as the formation of advanced glycation end products. Furthermore, aluminium, which also accumulates in neurofibrillary tangle-containing neurons, stimulates iron-induced lipid peroxidation. (2) Activated microglia, such as those that surround most senile plaques, are a source of NO and  $\text{O}_2$  which can react to form peroxynitrite, leaving nitrotyrosine as an identifiable marker. (3) Amyloid- itself has been directly implicated in reactive oxygen formation through peptidyl radicals. (4) Advanced glycation end products in the presence of transition metals can undergo redox cycling with consequent reactive oxygen species production.

Hydrogen Peroxide is a reactive oxygen species (ROS) generated in the stereoselective deamination of D-amino acids catalysed by D-amino acid oxidase enzyme (DAAO). Hydrogen peroxide readily crosses cellular membranes and damages DNA, proteins and lipids,



Intra-cellular  $\text{H}_2\text{O}_2$  generated by DAAO from D-amino acids can be reduced to hydroxyl radicals via transition metals catalyzed Haber-Weiss chemistry. Hydroxyl radical reacts with DNA, lipids and proteins inducing cell death. In a young healthy cell the  $\text{H}_2\text{O}_2$  produced can be removed by catalase in the peroxisomes or by glutathione peroxidase in the cytosol or plasma membrane. The GSH consumed in



the second reaction is regenerated by glutathione reductase using NADPH produced by the oxidative branch of the PPP as reducing equivalents. Inhibition of  $\gamma$ -glutamyl cysteine synthetase enzyme can deplete glutathione peroxidase

As the body ages optical isomers of amino acids very slowly undergo spontaneous, nonenzymatic racemization, so that over a very long period of time an equimolar mixture of the D and L isomers will be formed from the pure L or the pure D isomer. Each L-amino acid racemizes at a known rate at a given temperature. This fact can be used to determine the age of living people and animals or the age of fossil bones. For example, the L-aspartate of the protein dentine present in the outer hard enamel of the teeth, spontaneously racemizes at the rate of 0.10 percent per year at body temperature. Dentine contains only L-aspartate at the time the tooth is formed in childhood. The denture can be isolated from a single tooth of a person and its content of D-aspartate determined. Such analysis has been made on the denture of inhabitants of villages in Ecuador, where individuals claimed to be exceptionally long lived. This test yielded an age of 99 for a woman who was 97 years old by verified records.

So when we are born all our proteins and enzymes are made of 100% L-amino acids as we age the rate of D-amino acids present in the proteins and enzymes increase and since D-amino acids do not have biological activity they cause problems for the activity of enzymes and the integrity of structured peptides. The body including the brain neurons contain the enzyme DAAO (D-amino acid oxidase E.C. 1.4.3.3.) now this enzyme removes D-amino acids but in doing so produces highly toxic substances ie  $\text{NH}_3$  and  $\text{H}_2\text{O}_2$ . This production of  $\text{NH}_3$  and  $\text{H}_2\text{O}_2$  is counterbalanced in healthy cells by the production of enzymes such as catalase and glutathione peroxidase glutathione reductase and the enzyme of glutamylcysteine synthetase.

The enzyme that destroys D-amino acids in the cell are housed in ubiquitous cell organelles called peroxisomes along with a variety of other oxidase which produce  $H_2O_2$  during oxidation of their substrates. Peroxisome also contain catalase and other antioxidant enzymes which assist in the degradation of  $H_2O_2$ . The main characteristic of peroxisomes is their inducibility under exposure to certain drugs and xenobiotics. The increase in the number of peroxisomes observed in certain mammalian tissues is accompanied by a heterogeneous enhancement of the different peroxisomal enzyme activities mainly those of the oxidative system. While catalase shows weak induction 2 to fourfold the oxidative enzymes can be induced by between 20 to 30 fold. This imbalance between the induction of oxyradical producing oxidases and the induction of  $H_2O_2$  scavenging catalase and the glutathione system is the underlying flaw which is exacerbated by the ageing organs and the accumulation of D-amino acids in structural peptide and enzymes and ultimately leads to oxidative damage of DNA proteins and lipid peroxidation and which initiates normal degeneration and neoplastic transformation throughout the body. This would explain why several peroxisome proliferators are able to induce hepatocarcinoma in rodents and why chronic exposure to D-amino acids coupled with inhibition of the anti-oxidant enzyme systems of catalase and glutathione leads to neuronal death and the generation of amyloid plaques and dementia together with reduced efficiency in plasma transport metal carrier protein.

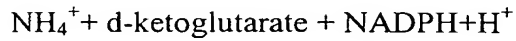
As the body ages the proteins and enzymes become more contaminated with D-amino acid groups and their efficiency suffers. This is particularly true of peptides which transport metals and this can lead, as we age, to increased copper and iron deposits in the liver and brain. Clinical features of increasing copper and iron deposits in the liver and brain consist of progressive choreoathetosis, dystonia, dysarthria, dementia, diabetes mellitus and retinal pigmentation. A structurally changed metal transport protein with D-amino acids in its structure may not take up copper from the digestive organs and bind it to

serum copper proteins as efficiently and these plasma proteins as they acquire increasing concentrations of D-amino acids in their structure may not oxidise Fe(II) to Fe(III). Many dementia patients initially report with an increased iron uptake in the brain and liver. The iron and copper deposits build up in the liver, pancreas, thyroid gland and in the brain especially. The principle areas of the brain effected are the caudate nucleus, basal ganglia, red nucleus and putamen. For example damage from free radicals has been demonstrated in susceptible neuronal populations in cases of Alzheimer's disease. In this case iron is a potent source of hydroxyl radical generation by the Fenton reaction with  $H_2O_2$ . Iron and copper deposits have been associated in many studies with senile plaques and neurofibrillary tangles - the pathological hallmark of many dementia conditions. The generation of  $H_2O_2$ , which reacts with these metal ions, is from the attempt by the brain's DAAO enzyme to clear the accumulating D-amino acid pool generated in the ageing brain. The second breakdown product of DAAO enzyme is ammonia ( $NH_3$ ) here we have a serious biochemical problem because ammonia is a very toxic substance particularly to the brain. Ammonia is so toxic that even very dilute solutions in the bloodstream can make an animal comatose. The toxicity of ammonia to the brain is not completely understood, but two major factors can be identified.

- (1) The pK of ammonia is quite high, so that at the pH of the blood it occurs almost entirely as ammonium ion ( $NH_4^+$ ).  $NH_4^+$  are not readily permeate through the plasma membrane or mitochondrial membranes.

However, free ammonia ( $NH_3$ ) a neutral molecule is freely permeant. Although only about 1% of the total ammonia in the blood occurs in the form of free  $NH_3$  at pH 7.4, this small amount can penetrate membranes and gain entry. Into brain cells and their mitochondria. The entry of ammonia into brain

mitochondria leads to the formation of glutamate from ammonia and d-ketoglutarate through the reverse action of glutamate dehydrogenase



The net result is that α-ketoglutarate is withdrawn from the pool of citric acid cycle intermediates in brain mitochondria, lowering the rate oxidation of glucose, the major fuel of the brain.

This inventor has discovered that Oltipraz is able to remove redox-active transition metals from AD brain sections. Given that there is little *in vivo* toxicity of the compound when used in a therapeutic setting, these data suggests a certain predication for the abnormally localized iron found in the disease as opposed to a total removal of all cellular iron. In fact, such a notion is supported by our preliminary data showing little/no neurotoxicity *in vitro* using doses of Oltipraz effective at chelating *in situ* or abolishing amyloid-β toxicity.

A major focus of AD-related basic and clinical research relates to the amyloid cascade hypothesis. Fundamental to this line of thinking is that amyloid-β is necessary for post mortem diagnosis, amyloid-β deposits are found in regions of the brain that are susceptible to the neurodegenerative processes, that production of amyloid-β is increased in all of the inherited forms of AD, and perhaps most convincing that *in vitro* amyloid-β is inherently toxic to neurons and clonal cell lines in culture. The neurotoxic activity of amyloid-β is dependent upon its aggregation into fibrils with a high content of β-sheet secondary structure and its toxic

mechanism is mediated by oxidative stress and that toxicity is attenuated by anti-oxidants. Recently, it has been found that the toxicity of amyloid- $\beta$  is mediated by iron in that toxicity was attenuated in a dose-dependent fashion by deferoxamine and restored, again in a dose-dependent fashion, by subsequent exogenous addition of ferrous iron (manuscript in preparation).

This inventor has discovered that when pre-incubated with amyloid- $\beta$ , Oltipraz has the ability to attenuate its toxicity in a dose-dependent manner similar to that of deferoxamine. Coupled together with our in situ demonstration that Oltipraz has the ability to function as a chelator of redox-active iron from sites of iron deposition in vivo, these findings strongly support the use of Oltipraz in chelation therapeutics for AD.

The method comprises incorporating the compound in a suitable pharmaceutical carrier, administering a therapeutically or prophylactically effective dosage of the compound incorporated in the carrier to a patient and employing the method in treating a patient for memory enhancement. Specifically note embodiment 97, 98 99 and 100. The method also includes therapeutically treating a patient for an illness selected from the group consisting of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia. This method may also treat other individuals that seek memory enhancement.

An example of a suitable pharmaceutical carrier is corn oil. The compounds of this invention incorporated into the pharmaceutical carrier may be administered to a patient by parenteral injection, such as for example, intravenously, intrathecally, intramuscularly or intraarterially.

Other potential routes of administration include, for example, orally, transdermally or by other means. The dosage of, route of, administration of, and duration of therapy with the compounds of this invention, which can readily be determined by those skilled in the art, will be individualized according to the illness being treated, body weight of the patient, other therapy employed in conjunction with the compounds of this invention and the condition, clinical response and tolerance of the patient.

It will be understood by those skilled in the art that the compounds described herein may be used as synergistic agents with neurosteroids and other compounds.

In order to effect the objects of this experiment this invention provides the use of oltipraz of this invention for memory enhancement and a method of using compounds, identified in the embodiments, in a patent for therapeutic and prophylactic purposes.

Whereas, particular embodiments of this invention have been described above for purposes of illustration, it will be evident to those skilled in the art that numerous variations of the details of the present invention may be made without departing from the invention as defended in the appended claims.

The present invention relates to a method of treatment of disorders of the central nervous system, in particular Parkinsons Disease, by the administration of compounds disclosed herein.

Parkinsons Disease is a disturbance of voluntary movement in which muscles become stiff and sluggish, movement becomes clumsy and difficult and uncontrollable rhythmic twitching of groups of muscles produces characteristic shaking or tremor. The condition is believed to be

caused by a degeneration of pre-synaptic dopaminergic neurones in the brain. The absence of adequate release of the chemical transmitter dopamine during neuronal activity thereby leads to the Parkinsonian symptomatology.

The compound of the present invention is useful in treating patients with Depressive Disorders and Bipolar Disorders. In the Diagnostic and Statistical Manual of Mental Disorders (Third Edition-Revised) ("DSM-III-R"), incorporated herein by reference, Depressive Disorders are defined as Major Depression, Dysthymia and Depressive Disorder NOS. We also include in this category Major Depressive Episode including Chronic Type, Melancholia, and Seasonal Pattern. Bipolar Disorders include Bipolar Disorder, Cyclothymia and Bipolar Disorder NOS.

A feature of Depressive Disorders is one or more periods of depression without a history of either Manic or Hypomanic episodes. A feature of Bipolar Disorders is the presence of one or more Manic or Hypomanic Episodes usually accompanied by one or more Major Depressive Episodes. A Manic or Hypomanic Episode is a distinct period during which the predominant mood is either elevated, expansive or irritable and there are associated symptoms of the Manic Syndrome as defined in DSM-III-R. The disturbance is severe enough to cause marked impairment in occupational or social functioning.

There are many ways to show that the compound of the present invention is useful in treating Depressive Disorders and Bipolar Disorders such as in animal models. See for example, "Animal Models as simulations of depression" by Paul Willner, *TiPS* 12:131-136 (April 1991); "Animal Models of Depression: An overview" by Paul Willner, *Pharmac. Ther.* 45:425-455 (1990), both of which are incorporated herein by reference. One such model is the Chronic Mild Stress Model.

Preferred pharmaceutical compositions are those suitable for enteral, especially oral, administration to warm-blooded animals. Daily dosages may be up to about 4 g, for example 500 mg to 4 g. The compositions may contain the active ingredient alone or in combination with a pharmaceutically acceptable excipient. The compositions may be in dosage unit forms such as tablets, coated tablets, hard or soft gelatin capsules or syrups. These can be prepared using known procedures, for example by conventional mixing, granulating, tablet coating, dissolving or lyophilising processes. Thus, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating the resulting mixture, and processing the mixture or granulate, if desired or necessary after the addition of suitable excipients, to give tablets or coated tablet cores.

Suitable excipients are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starches for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrants, such as the above mentioned starches, and also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate, and/or flow regulators and lubricants, for example silica, talc, stearic acid or salts thereof such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Coated tablet cores can be provided with suitable coatings, which if appropriate are resistant to gastric juices, using, inter-alia, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, shellac solutions in suitable



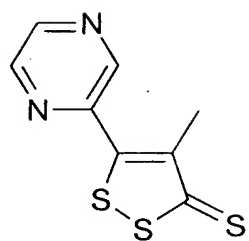
organic solvents or solvent mixtures or, for the preparation of coatings resistant to gastric Juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pignents can be added to the tablets or coated tablets, for example to identify or indicate different doses of active ingredient.

The present invention also provides pharmaceutically acceptable salts of compounds described in the attached embodiments as hereinbefore described, or precursors therefor as hereinbefore described, for use in a therapeutic method of treating a warm blooded animal body, for the treatment of indications such as aluminium overload, Alzheimer's disease, malaria, reperfusion injury, cancer and particularly in the treatment of ironoverload diseases. The present invention further provides the use of such salts or precursors for the preparation of a pharmaceutical composition for the treatment of the above mentioned indications, particularly iron-overload diseases.

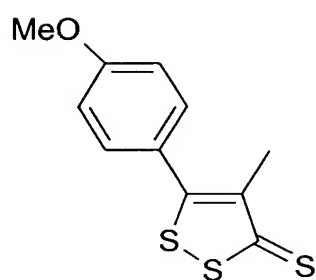
## EMBODIMENTS

1. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments

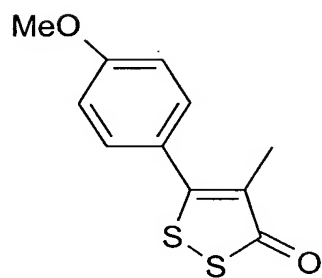
which comprises of one or more of the following compounds:



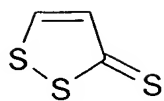
Oltipraz Fig 1



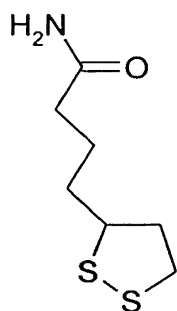
ADT - Fig 2



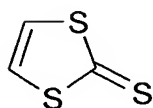
ADO - Fig 3



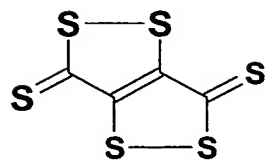
1,2-DITHIOLE 3-THIONE -  
Fig 4



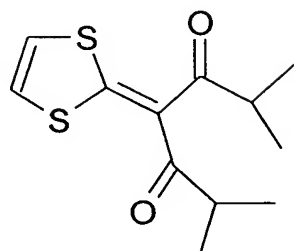
Lipoamide  
(1,2-dithiolane) - Fig 5



1,3-dithiole  
2-thione - Fig 6

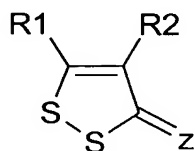


[1,2]Dithiolo[4,3-c]-1,2-dithiole-3,6-  
dithione Fig 6a

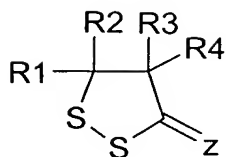


Malotilate - Fig 7

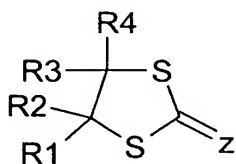
2. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following compounds



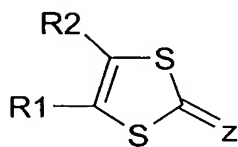
1,2-Dithiolane Class 1



1,2-Dithiole Class 2



1,3-Dithiole Class 3



1,3-Dithiolane Class 4

Wherein  $Z = S, O, NR, R_2, CR_2$  and Z can have the designations optionally and independently for all the classes. R in this case includes, H, alkyl(C1-C5), alkoxy (C1-C5) alkoxycarbonyl (C1-C5).  $R_2$  can form spiro rings about the ring carbon atom.

For the thiolane classes the ring carbon atoms can be doubly substituted.

R1-R4 are the main ring substituents for all classes and in order to cover a wide variety of substituents should include optionally and independently H, alkyl, aryl, heterocyclic, halogen, alkoxycarbonyl (C1-C5) or carboxyl.

R1, R2 or R3, R4 can form can form a spiro ring around the carbon atom to which they are attached or they can form fused or bridged rings to adjacent carbon atoms

The following definitions cover the majority of compounds.

Alkyl defined as C1-C10 linear or branched chain, saturated or unsaturated which can optionally singly or multiply substituted by halogen, alkyl (C1-C5), hydroxyl, alkoxy (C1-C5), alkoxycarbonyl, (C1-C5), carboxyl, amido, alkyl amido (C1-C5), amino, mono and dialkyl amino (C1-C5), alkyl carbamoyl (C1-C5), thiol, alkylthio (C1-C5) or benzenoid aryl.

Aryl defined as any optionally singly or multiply substituted benzenoid group (C6-C14).  
Substituents defined below.

Heterocyclic radical defined as any 4, 5 or 6 membered, optionally substituted heterocyclic ring, saturated or unsaturated, containing 1-3 ring atoms of which are N,O or S, the remaining ring atoms being carbon.

Substituents on the aryl or heterocyclic radical include:

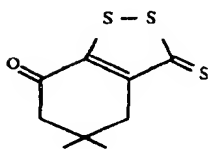
halogen, alkyl (C1-C5), hydroxyl, alkoxy (C1-C5), alkoxycarbonyl, (C1-C5), carboxyl, amido, alkyl amido (C1-C5), amino, mono and dialkyl amino (C1-C5), alkyl carbamoyl (C1-C5), thiol, alkyl thio (C1-C5) or benzenoid aryl, cyano, nitro, halo alkyls, alkylsulfonyl (C1-C5), sulfonate.

Two of such substituents can be part of a fused ring, which can be either saturated, or unsaturated, heterocyclic or carbo cyclic.

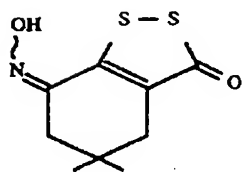
3. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder , Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron



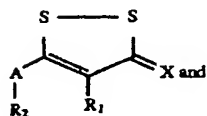
levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following compounds based on 1,2-dithiole-3-thione derivatives.



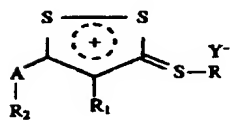
**Fig. 8**



**Fig . 9**



**Fig. 10**



**Fig. 11**

in which

X is chosen from

$=S,$

$=O,$

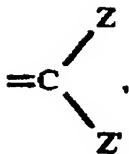
$=N-OH,$

$=N-R_5$

$R_5$ , being a  $C_1-C_6$  alkyl or an aryl group,

$=N-NH-CO-NH_2$  and

$=N-NH-CS-NH_2$ , and



Z and Z' being electron-attracting groups such as ester or cyano groups.

A is chosen from a  $>C=N-OH$  group. A group of formula  $>C=N-OR_3$ .

(where  $R_3$  is Chosen from hydroxyl, amino, chloro and  $C_1-C_4$ , alkoxy groups, an aryl( $C_1-C_6$  alkyl) group, a

( $C_1-C_6$  alkyl)Carbonl group and an aryl( $C_1-C_6$  alkyl)carbonyl group).

a may also be chosen from a  $>C=O$  group, a  $>C=N-R_4$ , group.  $R_4$  being a  $C_1-C_6$  alkyl group or an aryl group, and a  $CHOH$  group,

4. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following

Oximes of 1,2-dithiole-3-thione derivatives such as shown in figure 12, 13 & 14

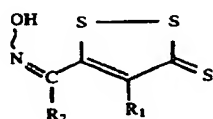


Fig 12

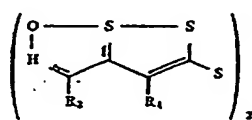


Fig 13

$R_1$  and  $R_2$  are chosen, independently of one another, from hydrogen, a halogen, a nitro group, a nitroso group, a thiocyno group, a  $C_1$ - $C_6$  alkyl group, a  $C_2$ - $C_6$  alkenyl group, an aryl group, aryl( $C_1$ - $C_6$  alkyl) group, an aryl ( $C_2$ - $C_6$  alkenyl) group, a carboxyl group, a ( $C_1$ - $C_6$  alkyl)carbonyl group, an arylcarbonyl group, a ( $C_1$ - $C_6$  alkoxy)carbonyl group, a ( $C_1$ - $C_6$  alkoxy)carbonyl ( $C_1$ - $C_6$  alkyl) group, a  $C_1$ - $C_6$  alkoxy group, a trifluoromethyl group, an amino group, a di( $C_1$ - $C_6$  alkyl) amino( $C_1$ - $C_6$  alkyl) group, an acylamino group of formula  $-NHCOC_nH_{2n+1}$  with  $n$  from 0 to 6, a group  $-NH-CSC_nH_{2n+1}$  with  $n$  from 0 to 6, a terpenyl group, a cyano group, a  $C_2$ - $C_6$  alkynyl group, a  $C_2$ - $C_6$  alkynyl group substituted with a  $C_1$ - $C_6$ , alkyl or an aryl group, a hydroxy( $C_1$ - $C_6$  alkyl) group, a ( $C_1$ - $C_6$  acyl) oxy ( $C_1$ - $C_6$  alkyl) group, a ( $C_1$ - $C_6$  alkyl) thio group and an arylthio group.

or alternatively  $R_1$  and  $R_2$  together form a mono- or polycyclic  $C_2$ - $C_{20}$  alkylene group optionally comprising one or more hetero atoms, with the exception of the 2,2dimethyltrimethylene group, or a  $C_3$ - $C_{12}$  cycloalkylene group.

$R$  is chosen from a  $C_1$ - $C_6$ , alkyl group, and their pharmaceutically acceptable salts,

In the foregoing definition, aryl group or aryl fraction of an arylalkyl group denotes an aromatic carbon-based group such as a phenyl or naphthyl group or an aromatic heterocyclic group such as a thienyl or furyl group it being possible for these groups to bear one or more substituents chosen from a halogen atom, a  $C_1$ - $C_4$  alkyl group, a  $C_1$ - $C_4$  alkoxy group, a trifluoromethyl group, a nitro group and a hydroxyl group.

Additionally Aldehydes or Ketones of previously identified compounds are incorporated such as shown in Fig. 15

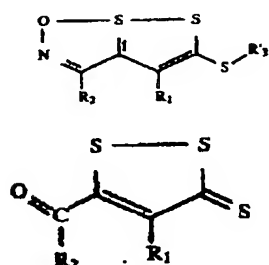


Fig 14

Fig. 15

5. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel

syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneruopathy, Major Depression, Dysthymia, Depressive Disorder , Major Depressive Episode including Chronic Type, Melancholis and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following compounds according to embodiment 3 wherein A (figure 10,11) is a group  $C=N-OR'_3$  where  $R'_3$  is an optionally substituted  $C_1-C_6$  alkyl group, in particular substituted with one or more groups chosen from hydroxyl, amino, chloro, bromo, fluoro, iodo and  $C_1-C_4$  alkoxy groups, or an aryl ( $C_1-C_6$ alkyl) group, that is to say compounds of formula

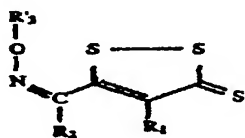


Fig. 16

OR

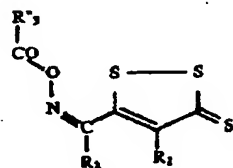


Fig. 18

in which  $R_3$  has the meaning given above

6. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following compounds as described in embodiment 3 (Fig 10 & 11) in which A is a group  $C=N-O-CO-R''_3$ ,  $R''_3$  being chosen from a hydrogen atom, an

optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl group, an aryl group and an aryl (C<sub>1</sub>-C<sub>6</sub> alkyl) group, that is to say compounds of formula

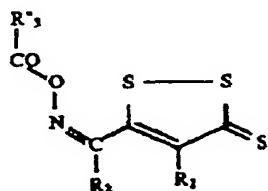


Fig 19

in which R''<sub>3</sub> being chosen from a hydrogen atom, an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl group, an aryl group.

Another group of compounds is formed by the compounds of embodiment 3 (Fig. 10 & 11) in which A is a CH--OH group, that is to say the compounds of formula

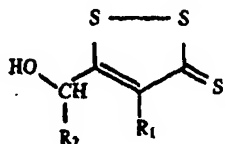


Fig 20

Another group of compounds is formed by the compounds of embodiment 3 (Fig. 10 & 11) in which A is a group C=N-R, R, being a C<sub>1</sub>-C<sub>6</sub> alkyl or an aryl group. that is to say compounds of formula



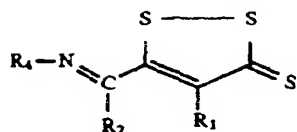


FIG 21

Another group of compounds include compounds of embodiment 3 (Fig 10 & 11) in which A is a  $C=O$  group and X is an oxygen atom, that is to say compounds of formula:

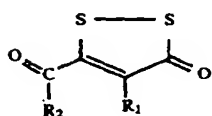


Fig 22

in which

$R_1$  is chosen from hydrogen, a halogen, a nitro group, a nitroso group, a thiccyano group, a  $C_1$ - $C_6$  alkyl group, a  $C_2$ - $C_6$  alkenyl group, an aryl group, an aryl ( $C_1$ - $C_6$  alkyl) group, an aryl ( $C_2$ - $C_6$  alkenyl) group, a carboxyl group, a ( $C_1$ - $C_6$  alkyl) carbonyl group, an arylcarbonyl group, a ( $C_1$ - $C_6$  alkoxy)carbonyl group, a ( $C_1$ - $C_6$  alkoxy) carbonyl ( $C_1$ - $C_6$  alkyl) group, a  $C_1$ - $C_6$  alkoxy group, a trifluoromethyl group, An amino group, a di ( $C_1$ - $C_6$  alkyl) amino ( $C_1$ - $C_6$  alkyl) group, an acylamino group of formula  $-NHCOC_nH_{2n+1}$  with  $n$  from 0 to 6, a group  $-NH-CSC_nH_{2n+1}$  with  $n$  from 0 to 6, a terpenyl group, a cyano group, a  $C_1$ - $C_6$  alkynyl group, a  $C_2$ - $C_6$  alkynyl group substituted with a  $C_1$ - $C_6$  alkyl or an aryl group, a hydroxy ( $C_1$ - $C_6$  alkyl) group,

a (C<sub>1</sub>-C<sub>6</sub> acyl)-oxy(C<sub>1</sub>-C<sub>6</sub> alkyl) group, a (C<sub>1</sub>-C<sub>6</sub> alkyl)thio group and an arylthio group.

R<sub>2</sub> is chosen from a nitro group, a nitroso group, a thiocyno group, a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>2</sub>-C<sub>6</sub> alkenyl group, an aryl group, an aryl (C<sub>1</sub>-C<sub>6</sub> alkyl) group, an aryl (C<sub>1</sub>-C<sub>6</sub> alkenyl) group, a carboxyl group, a (C<sub>1</sub>-C<sub>6</sub> alkyl)carbonyl group, an arylcarbonyl group, a (C<sub>1</sub>-C<sub>6</sub> alkoxy)carbonyl group, a (C<sub>1</sub>-C<sub>6</sub> alkoxy)carbonyl (C<sub>1</sub>-C<sub>6</sub> alkyl) group, a trifluoromethyl group, a di(C<sub>1</sub>-C<sub>6</sub> alkyl)amino(C<sub>1</sub>-C<sub>6</sub> alkyl) group, an acylamino group of formula -NHCOCH<sub>2</sub>nH<sub>2n+1</sub> with n from 0 to 6, a group -NH—CSC<sub>n</sub>H<sub>2n+1</sub> with n from 0 to 6, a terpenyl group, a cyano group, a C<sub>2</sub>-C<sub>6</sub> alkynyl group, a C<sub>2</sub>-C<sub>6</sub> alkynyl group substituted with a C<sub>1</sub>-C<sub>6</sub> alkyl or an aryl group, a hydroxy (C<sub>1</sub>-C<sub>6</sub> alkyl) group, a C<sub>1</sub>-C<sub>6</sub> acyl)-oxy(C<sub>1</sub>-C<sub>6</sub> alkyl) group, a (C<sub>1</sub>-C<sub>6</sub> alkyl)thio group and an arylthio group,

or alternatively R<sub>1</sub> and R<sub>2</sub> together form a mono- or polycyclic C<sub>2</sub>-C<sub>20</sub> alkylene group optionally comprising one or more hetero atoms

7. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid

and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following composition according to embodiment 6 in which  $R_2$  is chosen from  $C_1$ - $C_6$  alkyl  $C_2$ - $C_6$  alkenyl. aryl. aryl( $C_1$ - $C_6$  alkyl). aryl  $C_2$ - $C_6$  alkenyl. terpenyl.  $C_2$ - $C_6$  alkynyl.  $C_2$ - $C_6$  alkynyl substituted with  $C_1$ - $C_6$  alkyl or aryl.

8. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal

Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following composition according to embodiment 6 in *which* R is chosen from C<sub>1</sub>-C<sub>6</sub> alkyl.

9. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron

levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following compounds of formula shown in Figure 23

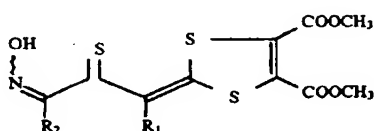


Fig. 23

$R_1$  and  $R_2$  are chosen, independently of one another, from hydrogen, a halogen, a nitro group, a nitroso group, a thiocyno group, a  $C_1$ - $C_6$  alkyl group, a  $C_2$ - $C_6$  alkenyl group, an aryl group, aryl( $C_1$ - $C_6$  alkyl) group, an aryl ( $C_2$ - $C_6$  alkenyl) group, a carboxyl group, a ( $C_1$ - $C_6$  alkyl)carbonyl group, an arylcarbonyl group, a ( $C_1$ - $C_6$  alkoxy)carbonyl group, a ( $C_1$ - $C_6$  alkoxy)carbonyl ( $C_1$ - $C_6$  alkyl) group, a  $C_1$ - $C_6$  alkoxy group, a trifluoromethyl group, an amino group, a di( $C_1$ - $C_6$  alkyl) amino( $C_1$ - $C_6$  alkyl) group, an acylamino group of formula  $-NHCOC_nH_{2n+1}$  with  $n$  from 0 to 6, a group  $-NH-CSC_nH_{2n+1}$  with  $n$  from 0 to 6, a terpenyl group, a cyano group, a  $C_2$ - $C_6$  alkynyl group, a  $C_2$ - $C_6$  alkynyl group substituted with a  $C_1$ - $C_6$ , alkyl or an aryl group, a hydroxy( $C_1$ - $C_6$  alkyl) group, a ( $C_1$ - $C_6$  acyl) oxy ( $C_1$ - $C_6$  alkyl) group, a ( $C_1$ - $C_6$  alkyl) thio group and an arylthio group.

or alternatively  $R_1$  and  $R_2$  together form a mono- or polycyclic  $C_2$ - $C_{20}$  alkylene group optionally comprising one or more hetero atoms.

R is chosen from a  $C_1$ - $C_6$ , alkyl group, and their pharmaceutically acceptable salts,

In the foregoing definition, aryl group or aryl fraction of an arylalkyl group denotes an aromatic carbon-based group such as a phenyl or naphthyl group or an aromatic heterocyclic group such as a thienyl or furyl group. it being possible for these groups to bear one or more substituents chosen from a halogen atom, a  $C_1$ - $C_4$  alkyl group, a  $C_1$ - $C_4$  alkoxy group, a trifluoromethyl group, a nitro group and a hydroxyl group.

10. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneruopathy, Major Depression, Dysthymia, Depressive Disorder , Major Depressive Episode including Chronic Type, Melancholis and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g.

neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following isobenzothiazolone derivative having the structure:

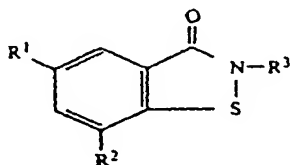


Fig 24

In this structure at least one of  $R^1$  and  $R^2$  is preferably nitro, arylazo, substituted arylazo, benzylideneamino or substituted benzylideneamino. When only one of  $R^1$  and  $R^2$  is so substituted, one of  $R^1$  and  $R^2$  may be hydrogen. The  $R^3$  substituent is selected from alkyl groups in less than about 7 carbon atoms, amino, hydroxyl, alkoxy, and aryl groups (and functionalized forms thereon,)

Preferred species of the isobenzothiazole derivative of the present invention comprise  $R^1$  as nitro or arylazo and  $R^2$  as hydrogen, for example. Examples include compounds where  $R^2$  is hydrogen and  $R^1$  is phenylazo; substituted arylazo such as 4-hydroxyphenylazo; 4--nitro-2-methylphenylazo; 2-hydroxy-1-naphthylazo; 2- hydroxy-5-methylphenylazo; 2-hydroxy-4-methyl-5-nitrophenylazo; 4-hydroxy-1-naphthylazo; 4-hydroxy-3-methyl- 1 -naphthylazo; 4-hydroxy-5-aza-1 -naphthylazo; 2-amino-1-naphthylazo; 1-hydroxy-2-naphthylazo;

3-N,Ndimethylaminopropylcarboxyamido-1-hydroxy-4-naphthylazo;  
 1-hydroxy-4-methoxy-2-naphthylazo, 2-hydroxy-3-carboxy-1-naphthylazo; 1-hydroxy-3, 6-disulfonato-2-naphthylazo; 2, 3-dihydroxy-1-naphthylazo; or 2-hydroxy-3, 5-dimethyl-1-phenylazo. In one particular embodiment  $R^1$  is the substituted benzylideneamino, 2,4-dinitrobenzylideneamino and  $R^2$  is hydrogen. Additionally  $R^1$  as hydrogen and  $R^2$  as 2-hydroxy-1-naphthylazo or 4-hydroxy-1-phenylazo.

In one aspect,  $R^3$  substituents with sufficient polarity to confer aqueous solubility upon the compound. For example,  $R^3$  may be  $-(CH_2)_nR^4R^5$  where  $n$  is from 2 to 6 and  $R^4$  and  $R^5$  are simple alkyls or hydrogens. Other possible water solubilizing side chains include 3-carboxypropyl, sulfonatoethyl and polyethyl ethers of the type  $-CH_2(CH_2OCH_2)_nCH_3$  where  $n$  is less than 10. Preferred compounds include  $R^3$  side chains containing aminoalkyl, carboxyalkyl, omega amino polyethyl ethers and N-haloacetyl derivatives. In a broader sense, for various utilities  $R^3$  may be alkyl, aryl, heteroaryl, alkoxy, hydroxy or amino groups. When including substitutions for solubility or reactivity purposes,  $R^3$  may be aminoalkyl, carboxyalkyl, hydroxyalkyl or haloalkyl. The aryl or heteroaryl  $R^3$  moieties may be substituted, for example as aminoaryl, carboxyaryl or hydroxyaryl.

11. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated



with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following Isobenzothiazolone derivative having the structure:

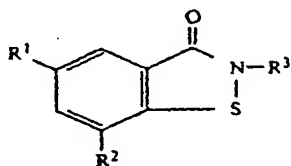


Fig 25

wherein at least one of  $R^1$  and  $R^2$  is nitro, arylazo, substituted arylazo, benzyldeneamino or substituted benzyldeneamino and one of  $R^1$  and  $R^2$  may be hydrogen and  $R^3$  is an aminoalkyl, aminoaryl and aminoheteroaryl, carboxyalkyl, carboxyaryl or carboxyheteroaryl covalently linked to a polymer comprising amino or hydroxy groups. The spacer arm  $R^3$  can comprise oligomers or polyethylene-glycol and its derivatives. In one aspect,  $R^3$  may be 17-chloroacetamido-3,6,9,12, 15-pentaoxyheptadecyl

where hexaethylene glycol has been chloroacetamidated. When the polymer groups,  $Y^1$  and  $R^3$  comprises carboxyl groups, the covalent linkage is preferably through an ester bond. When the polymer comprises amino groups, the analog covalent linkage is through an amide bond. The aminebearing polymer, when coupled to  $R^3$ , may be a polymer such as chitosan, polyalkylamine, aminodextran, polyethyleneimine, polylysine or amityrene.

The  $R^3$  substituents of the present invention may also comprise an alkyl linked to an aminebearing polymer by amine displacement of a halogen from an alpha-haloalkyl or alpha-haloalkylcarbox amido  $R^3$  precursor. In the case of aminoalkyl or aminoaryl groups the  $R^3$  substituent may also be covalently linked to a polymer such as polyepichlorohydrin, chloromethylpolystyrene, polyvinylalcohol or polyvinylpyridine. The  $R^3$  substituent of the present invention may generally be an aminoalkyl, hydroxyalkyl, aminoaryl or hydroxyaryl group linked to a polymer comprising carboxyl groups through amide or ester linkages.

When polymers are involved in the  $R^3$  structure, the polymer may be one such as polyacrylic acid, polymethacrylic acid, polyitaconic acid, oxidized polyethylene oxide, poly(methylmethacrylate/methacrylic acid), carboxyinethyl cellulose, carboxymethyl agarose or carboxymethyl dextran. When such a carboxyl polymer is involved, the  $R^3$  may be aminoalkyl (such as 8 aminohexyl, for example), hydroxyalkyl, aminoaryl or hydroxyaryl linked to the polymer through amide or ester linkages. In such cases, an  $R^3$  precursor function may bear an amine or hydroxyl group to be covalently linked to a polymer by reaction with an acid anhydride-

bearing polymer or by coupling with a carboxylatebearing polymer through carbodimideinduced bond formation.

The R<sup>3</sup> substituent or precursor thereto in the compound of the present invention may also be a haloalkyl or carboxylialoalkyl moiety such as chloracetamido. Such a substituent may readily coupled to an aminebearing polymer by amine displacement of the halogen.

"Aryl," as used herein, is intended to include organic residues derived from aromatic hydrocarbon or aromatic heterocyclic ring systems. Accordingly aryl groups include the unsubstituted ring residues such as phenyl and naphthyl and substituted forms thereof. Heterocyclic or heteroaryl residues may be those comprising one or more heteroatoms (e.g., nitrogen, oxygen, sulfur) in the ring system such as pyridyl, oxazolyl, quinoly), thiazolyl and substituted forms thereof.

"Alkyl," as used herein, is intended to include aliphatic and cyclic organic residues having a carbon at a point of attachment. Accordingly, alkyl groups include unsubstituted hydrocarbon residues of the formula C<sub>n</sub> H<sub>2n+1</sub> and substituted and cyclic forms thereof. Such hydrocarbons are usually of the lower alkyl class which have six carbons or less. It is understood that larger alkyl groups may be used. Alkyl includes substituted residues which are intended to include the hydrocarbon residues bearing one or more, same or different, functional groups as described below.

The alkyl and aryl group previously described may be substituted with functional groups. Such functional groups include essentially all chemical groups which can be introduced synthetically and result in stable compounds. Examples of these functional groups are hydroxyl, halogen

(fluoro, chloro, bromo), amino (including alkylamino and dialkylamino), cyano, nitro, carboxy (including carbalkoxy), carbamoyl (including N and N,N alkyl), sulfb, alkoxy, alkyl, aryl, and arylazo.

12. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, which comprises of one or more of the following compounds

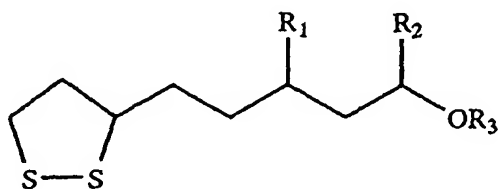
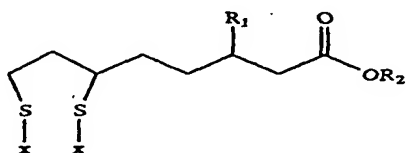


Fig 26

wherein  $R_1$  and  $R_2$  are independently (=0) or -OR, where R is H or (C<sub>1</sub>-C<sub>4</sub>) alkyl; and  $R_3$  is H or (C<sub>1</sub>-C<sub>4</sub>) alkyl. Preferably,  $R_3$  is H. Preferably  $R_1$  and  $R_2$  are (=0) or OH.

13. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis a Fig 27 el syndrome, Major Depression, Dysthymia, Depressive Disorder , Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, which comprises of one or more of the following compounds



wherein X is H or both Xs represent a direct bond between the two sulfur atoms;  $R_1$  is (=O) or -OH; and  $R_2$  is H, Na, K or (C<sub>1</sub>-C<sub>4</sub>)alkyl

In particular the compound maybe 3-keto lipoic acid, 3-hydroxy lipoic acid, 3-keto dihydrolipoic acid or 3-hydroxy dihydrolipoic acid.

14. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneruopathy, Major Depression, Dysthymia, Depressive Disorder , Major Depressive Episode including Chronic Type, Melancholis and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following

1,2-dithiol-3thione derivative of a formula shown in Fig. 28

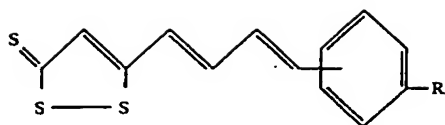


Fig. 28

wherein R denotes hydrogen, halogen, lower alkoxy group, lower alkyl group, amino group, lower alkylsubstituted amino group or lower alkoxy carbonyl group.

In the above-described formula Fig 28, the term "lower" means methyl, ethyl, propyl and butyl, as well as its structural isomers such as isopropyl, isobutyl and tertiarybutyl.

Among the compounds of the formula shown in Figure 28, preferred compounds include

5-(4-phenyl-1,3-butadienyl)-1,2-dithiol-3-thione,

5-(4-(4-chlorophenyl)-1,3-butadienyl)-1,2-dithiol-3-thione,

5-{4-(4-methoxyphenyl)-1,3-butadienyl}-1,2-dithiol-3-thione,

5-{4-(p-toluy)-1,3-butadienyl}-1,2-dithiol-3-thione,

5-{4-(o-chlorophenyl)-1,3-butadienyl}-1,2-dithiol-3-thione, and 5-{4-(m-methylphenyl)-1,3-butadienyl}-1,2-dithiol-3-thione

The following compounds are also included:

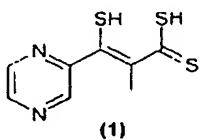


Fig 29

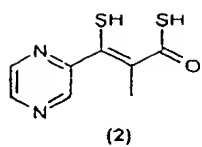


Fig 30

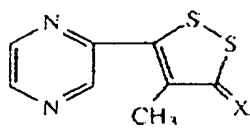


Fig 31

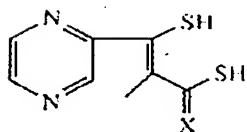


Fig 31a

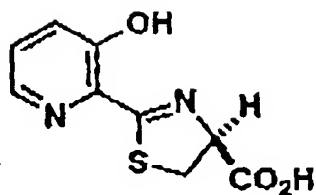


Fig 32

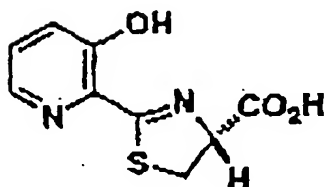


Fig. 33



15. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneruopathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following; 1,2-dithiole of the formula (Fig 34).



Fig 34

wherein Het represents pyrimidin-2-yl, pyrimidin-4-yl, or pyrimidin-5-yl, or a said pyrimidin-2-yl, pyrimidin-4-yl or pyrimidin-5-yl substituted by halogen, alkyl of 1 through 4 carbon atoms, alkoxy of 1 through 4 carbon atoms, mercapto, alkylthio of 1 through 4 carbon

atoms, or dialkylamino having 1 through 4 carbon atoms in each alkyl, and R represents halogen, alkyl of 1 through 4 carbon atoms, alkyl of 1 through 4 carbon atoms substituted by alkoxycarbonyl having 1 through 4 carbon atoms in the alkoxy, carboxy, alkoxycarbonyl having 1 through 4 carbon atoms in the alkoxy, carbamoyl, N-alkylcarbamoyl having 1 through 4 carbon atoms in the alkyl, or R,-CH(OH)- in which R, represents hydrogen or alkyl of 1 through 3 carbon atoms.

16. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following

dithiole compounds according to embodiment 15 wherein Het represents pyrimidin-2-yl, pyrimidin-4-yl, or pyrimidin-5-yl, or pyrimidin-2-yl, pyrimidin-4-yl, or pyrimidin-5-yl substituted by halogen, alkyl of 1 through 4 carbon atoms, alkoxy of 1 through 4 carbon atoms, alkylthio of 1 through 4 carbon atoms, or dialkylamino having 1 through 4 carbon atoms in each alkyl], and R represents alkyl of 1 through 4 carbon atoms, carboxy, alkoxycarbonyl having 1 through 4 carbon atoms in the alkoxy, carbamoyl, or N-alkylcarbamoyl having 1 through 4 carbon atoms in the alkyl.

17. A method for the treatment according to embodiment 15 wherein Het represents pyrimidin-2-yl, pyrimidin-4-yl, or pyrimidin-5-yl, or pyrimidin-2-yl, pyrimidin-4-yl or pyrimidin-5-yl substituted by halogen, alkyl of 1 through 4 carbon atoms, alkylthio of 1 through 4 carbon atoms, or dialkylamino having 1 through 4 carbon atoms in each alkyl], and R represents alkyl of 1 through 4 carbon atoms, alkoxycarbonyl having 1 through 4 carbon atoms in the alkoxy, or R,-CH(OH)- in which RI represents hydrogen or alkyl of 1 through 3 carbon atoms.

18. A method for the treatment according to embodiment 15 wherein the compound is 4-ethyl-5-(pyrimidin-5-yl)-1,2-dithiole-3-thione.

19. A method for the treatment according to embodiment 15 wherein the compound is 4-methyl-5-(5-methylthiopyrimidin-4-yl)-1,2-dithiole-3-thione.

20. A method for the treatment according to embodiment 15 wherein the compound is 5-(5-chloropyrimidin-4-yl)-4-methyl-1,2-dithiole-3-thione.

21. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following 1,2-dithiol-3-thion-S-oxide compound (Figure 35)

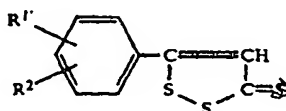


Fig 35

wherein

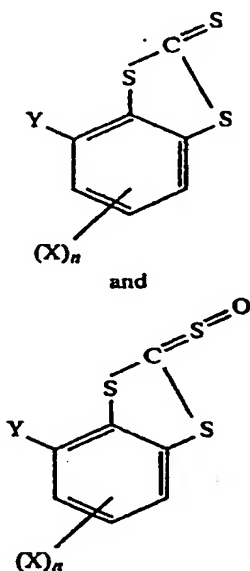
R<sub>1</sub> represents alkyl with 1-4 carbon atoms, lower alkoxy, hydroxy, halogen, trifluoromethyl or nitro, and R<sub>2</sub> represents hydrogen, halogen or lower alkoxy, or

R<sub>1</sub> and R<sub>2</sub> are bonded to adjacent carbon atoms and together form an alkylene dioxy group with 1-2 carbon atoms.

22. A method for the treatment according to embodiment 21, wherein R<sub>1</sub> is selected from the group consisting of fluorine, chlorine, Bromine, iodine and methoxy, and R<sub>2</sub> is hydrogen.

23. A method for the treatment of depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneruopathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholis and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future

memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following compounds selected from the group consisting of those of the formulae:



wherein Y is selected from nitro and trifluoromethyl; X is selected from alkyl and alkenyl of up to 6 carbon atoms, nitro, trichloromethyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfoxyl, trifluoromethylsulfonyl, methoxymethyl, cyano, carboxy, halogen (F, Cl, Br, I), hydroxy, acetylamino, amino, N-phenylamino, N,N-diallylamino, alkoxy, N-morpholino, N-piperidino, N-piperazino, N-pyrrolidino, dimethylaminodithiocarbamyl, carboalkoxy, alkylthio, mono- and dialkylamino, N-alkylcarbamyl, N,N-dialkylcarbamyl, alkylsulfoxy,

alkylsulfonyl, said alkyl groups containing from 1 to 4 carbon atoms; n is an integer from 1 to 3 wherein at least one of said X groups is selected from N-morpholino, N-piperidino, N-piperazino or N-pyrrolidino; and salts thereof.

24. A method of treatment according to embodiment 23 wherein Y is nitro and n is 1.

25. A method of treatment according to embodiment 23 wherein Y is trifluoromethyl and n is 1.

26. A method of treatment according to embodiment 23 wherein Y is trifluoromethyl and n is 2.

27. A method of treatment according to embodiment 23 wherein Y is nitro and n is 2.

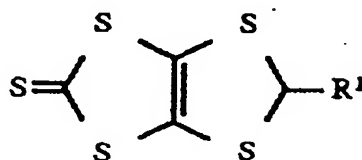
28. A method of treatment according to embodiment 23 wherein Y is CF<sub>3</sub> and n is 2.

29. A method of treatment according to embodiment 23 wherein Y is CF<sub>3</sub> and n is 2.

30. The compound according to embodiment 29 which is  
S-tert.butyl-S'-(2,4-dinitro-3-aminopropyl-6-tri-fluoromethylphenyl)-trithiocarbonate.

32. A pharmaceutical formulation for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and

Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following 1,3-dithiolo(4.5-d)-1,3-dithiino-2-thione compound corresponding to the formula:



wherein R' represents -H, -Br, -Cl, -F, I, -CN or  $-\text{CH}_2(\text{CH}_2)_n\text{CH}_3$  and n is an integer of from 0 to 14.

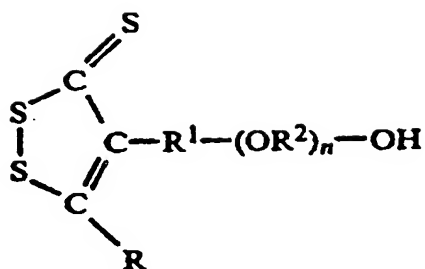
32. A method of embodiment 31 wherein the compound is 1,3-dithiolo(4.5-d)-1,3-dithiolo-2-thione.
33. A method of embodiment 31 wherein the compound is 5-chloro-1,3-dithiolo(4.5-d)-1,3-dithiolo-2-thione.



34. A method of embodiment 31 wherein the compound is

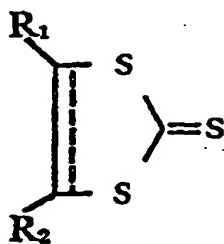
5-cyano-13-dithiolo(4.5-d)-1,3-dithiole-2-thione.

35. A pharmaceutical formulation for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following amount of a water soluble compound of the formula:



wherein R is H or a C<sub>1</sub> to C<sub>12</sub> alkyl moiety; R<sub>1</sub> is a C<sub>6</sub> to C<sub>12</sub> arylene moiety; R<sub>2</sub> is a C<sub>1</sub> to C<sub>4</sub> alkylene moiety; and n is 2 to 50.

36. A method for the treatment of depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneruopathy, Major



Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including

Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following cyclic sulfur-containing compound represented by the following formula;

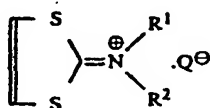
wherein the dotted line is optionally present and wherein the groups  $R_1$  and  $R_2$  are independently selected from the group consisting of hydrogen;  $C_{1-20}$  alkyl groups and  $C_{2-12}$  alkenyl groups.

37. A method according to embodiment 36, wherein  $R_1$  and  $R_2$  are independently selected from the group consisting of hydrogen,  $C_{1-4}$  alkoxy groups, and  $C_{2-4}$  alkenyl groups.

38. A method according to embodiment 36, wherein  $R_1$  and  $R_2$  are each hydrogen.

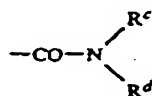
39. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia,

senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following amount of a compound of the formula 1,3-dithiole derivative having the formula:



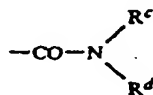
wherein R<sub>1</sub> and R<sub>2</sub> together form an alkylene or alkenylene group having from 3 to 6 carbon atoms, or a hetero atom selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom which may have a substituent selected from the group consisting of a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a lower alkoxycarbonyl group, a hy-

droxy-substituted lower alkyl group, an aryl group and an aralkyl group, and said alkylene or alkenylene group substituted by one or two substituents selected from the group consisting of a lower alkyl group, a carboxyl group, a lower alkoxy carbonyl group, and a



group wherein each of  $\text{R}^c$  and  $\text{R}^d$  is a hydrogen atom, a lower alkyl group, an aryl group or an aryl group,

provided that at least one substituent on the alkylene or alkenylene group is a carboxyl, loweralkoxy carbonyl or



group, and Q is an acid residue.

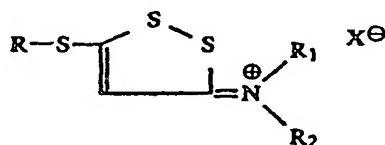
40. The 1,3-dithiole derivative according to embodiment 39, wherein  $\text{R}^1$  and  $\text{R}^2$  together form  $\text{--(CH}_2)_4\text{--}$ ,  $\text{--(CH}_2)_5\text{--}$ ,  $\text{--(CH}_2)_6\text{--}$ ,  $\text{--CH}_2\text{OCH}_2\text{CH}_2\text{--}$ ,  $\text{--CH}_2\text{SCH}_2\text{CH}_2\text{--}$ ,  $\text{--CH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2\text{--}$ ,  $\text{--CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{--}$ ,  $\text{--CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{--}$ ,  $\text{--CH}_2\text{CH}_2\text{N(ph)}_2\text{CH}_2\text{CH}_2\text{--}$ ,  $\text{--CH}_2\text{CH}_2\text{N(CH}_2\text{ph)CH}_2\text{CH}_2\text{--}$ ,  $\text{--CH}_2\text{CH}_2(\text{CH}_3)\text{CH}_2\text{CH}_2\text{--}$ ,  $\text{--CH}_2\text{CH=CHC--H}_2\text{--}$ ,  $\text{CH}_2\text{CH=CHCH}_2\text{CH}_2\text{--}$ , which may be substituted by carboxyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, N-phenylcarbamoyl or N-benzylcarbamoyl, and Q

is an acid residue of hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, perchloric acid, borofluoric acid, sulfuric acid, phosphoric acid, oxalic acid, tartaric acid, citric acid, methanesulfonic acid or p-toluenesulfonic acid.

41. The 1,3-dithiole derivative according to embodiment 39, wherein the moiety is 2-ethoxycarbonylpyrrolidinium, 2-carboxypyrrolidinium, 2-carbamoylpyrrolidinium, 4-ethoxycarbonylthiazolidinium, 2-ethoxycarbonylpiperidinium, 3-ethoxycarbonylpiperidinium, 4-ethoxycarbonylpiperidinium, 4-carboxypiperidinium, 4-carbamoylpiperidinium, 3-ethoxycarbonyl-6-methyl piperidinium or 4-ethoxycarbonylpiperazinium, and Q is C10<sub>4</sub>, Cl, Br, I or HS0<sub>4</sub>.

42. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia,

Schizophreniform Disorder, Delusional Disorder, or Phychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments which comprises of one or more of the following compounds selected from the group consisting of those of the formula: 1,2-dithiol-3-ylideneammonium derivative of the general formula:



wherein  $\text{X}^\ominus$  represents an pharmaceutically acceptable anion, R represents a straight- or branched-chain alkyl radical containing 1 to 7 carbon atoms [unsubstituted or substituted by a hydroxy, carboxy, alkoxycarbonyl, cyano, dialkylamino or alkylcarbonyl radical, or a benzoyl radical the phenyl ring of which is unsubstituted or substituted by one or more halogen atoms or radicals selected from alkyl (optionally substituted by one or more halogen atoms), alkoxy, hydroxy, amino, alkylamino, dialkylarnino, cyano, and nitro, or by a thenoyl radical the thienyl ring of which , is. unsubstituted or substituted by one or more halogen atoms or radicals selected from alkyl, cyano and nitro, or a pyridylcarbonyl, carbamoyl, dialkylcarbamoyl (the alkyl radicals of which can together form, with the nitrogen atom to which they are attached, a 5- or 6-membered heterocyclic ring optionally

containing another heteroatom selected from oxygen, sulphur, and nitrogen substituted by an alkyl or alkylcarbonyl radical) or pyridyl radical], a dialkylcarbamoyl radical (the alkyl radicals of which can together form, with the nitrogen atom to which they are attached, a 5- or 6-membered heterocyclic ring optionally containing another heteroatom selected from oxygen, sulphur, and nitrogen substituted by an alkyl or alkylcarbonyl radical), an alkenyl radical, containing 2 to 6 carbon atoms, an alkynyl radical containing 2 to 6 carbon atoms, or an alkoxycarbonyl radical, or alternatively represents a , 2-oxotetrahydrofuran-3-yl or 2-oxotetrahydropyran-3-yl ring, and either R<sub>1</sub> and R<sub>2</sub> which have the same or different significances each represent a phenyl radical, a cycloalkyl radical containing 3 to 7 carbon atoms, or an alkyl or phenylalkyl radical, or alternatively together form, with the nitrogen atom to which they are attached a 5-, 6- or 7-membered heterocyclic ring which can optionally contain another hetero-atom selected from oxygen, sulphur, and nitrogen substituted by an alkyl radical, or R<sub>1</sub> represents a phenyl radical unsubstituted or unsubstituted by one or more halogen atoms or radicals selected from alkyl (optionally substituted by one or more halogen atoms), alkoxy, hydroxy, amino, alkylamino, dialkylamino, cyano and nitro, or alternatively represents a cycloalkyl radical containing 3 to 7 carbon atoms, or an alkyl or phenylalkyl radical, and R<sub>2</sub> represents a hydrogen atom, and also the corresponding bases when R<sub>2</sub> represents a hydrogen atom, the aforementioned alkyl and alkoxy radicals and moieties containing 1 to 4 carbon atoms in a straight- or branched-chain unless otherwise indicated.



43. A compound according to embodiment 42 wherein  $X\theta$  represents a pharmaceutically acceptable anion, R represents a straight- or branched-chain alkyl radical containing 1 to 7 carbon atoms [unsubstituted-or substituted by hydroxy, carboxy, alkoxycarbonyl, cyano, dialkylamino, alkylcarbonyl, benzoyl, thenoyl, pyridyl, carbonyl, carbamoyl, dialkylcarbamoyl (the alkyl radicals of which can together form, with the nitrogen atom to which they are attached, a 5- or 6-membered heterocyclic ring optionally containing another hetero-atom selected from oxygen, sulphur, and nitrogen substituted by an alkyl or alkylcarbonyl radical) or pyridyl radical], a dialkylcarbamoyl radical (the alkyl radicals of which can together form, with the nitrogen atom to which they are attached, a 5- or 6-membered heterocyclic ring optionally containing another hetero-atom selected from oxygen, sulphur, and nitrogen substituted by an alkyl or alkylcarbonyl radical), an alkenyl radical containing 2 to 6 carbon atoms or an alkynyl radical containing 2 to 6 carbon atoms, and either  $R_1$  and  $R_2$ , which have the same or different significances, each represent a phenyl radical, a cycloalkyl radical containing 3 to 7 carbon atoms, or an alkyl or phenylalkyl radical or alternatively together form, with the nitrogen atom to which they are attached, a 5-, 6- or 7-membered heterocyclic ring which can optionally contain another hetero-atom selected from oxygen, sulphur, and nitrogen substituted by an alkyl radical, or  $R_1$  represents a phenyl radical a cycloalkyl radical containing 3 to 7 carbon atoms, or an alkyl or phenylalkyl radical, and  $R_2$  represents a hydrogen atom, and also the corresponding bases when  $R_2$  represents hydrogen, the aforementioned alkyl and alkoxy radicals and moieties containing 1 to 4 carbon atoms in a straight or branched-chain unless otherwise mentioned.

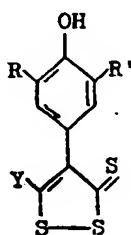
44. A compound according to embodiment 42 wherein  $X\theta$  represents a pharmaceutically acceptable anion, R represents an alkenyl radical containing 2 to 6 carbon atoms, or a

straight- or branched-chain alkyl radical containing 1 to 7 carbon atoms [unsubstituted or substituted by a cyano, dialkylamino, carbamoyl, alkylcarbonyl or thenoyl radical, or a benzoyl radical the phenyl ring of which is unsubstituted or substituted by one or more halogen atoms or radicals selected from alkyl, alkoxy, hydroxy and, cyano], the aforementioned alkyl and alkoxy radicals and moieties containing 1 to 4 carbon atoms in a straight- or branched-chain unless otherwise stated, and R<sub>1</sub> and R<sub>2</sub> together with the nitrogen atom to which they are attached represent a pyrrolidin-1-yl or morpholino radical.

45. A compound according to embodiment 42 wherein X<sup>0</sup> represents a pharmaceutically acceptable anion, R represents a methyl or ethyl radical unsubstituted or substituted by a benzoyl radical the phenyl ring of which is unsubstituted or substituted by one or more halogen atoms or radicals selected from alkyl and alkoxy radicals containing 1 to 4 carbon atoms in a straight- or branched-chain, and the hydroxy and cyano radical and R<sub>1</sub> and R<sub>2</sub> together with the nitrogen atom to which they are attached represent the morpholino radical.
46. A 1,2-dithio-1-3-ylideneammonium derivative according to embodiment 42 which is -[5-(4-chlorophenacylthio)-1,2-dithiol-3-ylidene] morpholinium chloride.
47. A 1,2-dithiol-3-ylideneammonium derivative according to embodiment 42 which is N-[5-(3-methoxyphenacylthio)-1,2-dithiol-3-ylidene]-morpholinium chloride.
48. A 1,2-dithiol-3-ylideneammonium derivative according to embodiment 42 which is N-[5-(4-fluorophenacylthio)-1,2-dithiol-3-ylidene]-morpholinium chloride.
49. A 1,2-dithiol-3-ylideneammonium derivative according to embodiment 42 which is N-[5-(2,4-dichlorophenacylthio)-1,2-dithiol-3-ylidene]-morpholinium chloride.

50. A 1,2-dithiol-3-ylideneammonium derivative according to embodiment 42 which is N-[5-(2-chlorophenacylthio)-1,2-dithiol-3-ylidene]-morpholinium iodide.
51. A 1,2-dithiol-3-ylideneammonium derivative according to embodiment 42 which is N-[5-(4-hydroxyphenacylthio)-1,2-dithiol-3-ylidene]-morpholinium chloride.
52. A 1,2-dithiol-3-ylideneammonium derivative according to embodiment 42 which is N-[5-(4-methoxyphenacylthio)-1,2-dithiol-3-ylidene]-morpholinium iodide.
53. A 1,2-dithiol-3-ylideneammonium derivative according to embodiment 42 which is N-[5-(4-methylphenacylthio)-1,2-dithiol-3-ylidene]-morpholinium chloride.
54. A 1,2-dithiol-3-ylideneammonium derivative according to embodiment 42 which is N-[5-(4-cyanophenacylthio)-1,2-dithiol-3-ylidene]-morpholinium chloride.
55. A 1,2-dithiol-3-ylideneammonium derivative according to embodiment 42 which is N-[5-(phenacylthio)-1,2-dithiol-3-ylidene]-morpholinium chloride.
56. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional

Disorder, or Phychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments comprising a compound of the formula



in which R and R1 are the same or different and each is an alkyl radical having from 1 to 12 carbon atoms, a cycloalkyl radical having from 5 to 12 carbon atoms which may be substituted with alkyl groups having from 1 to 4 carbon atoms or an aralkyl radical having from 7 to 14 carbon atoms, and Y is hydrogen, mercapto or SW where R' is an alkyl radical having from 1 to 20 carbon atoms, cycloalkyl having from 5 to 12 carbon atoms, alkenyl from 3 to 20 carbon atoms, or aralkyl having from 7 to 14 carbon atoms.

57. A compound according to embodiment 56 in which R and R1 are branched-chain alkyl radicals having from 3 to 8 carbon atoms, 1-methyl cyclohexyl or aa-dimethyl benzyl.

58. A compound according to embodiment 56 in which Y is an -S-alkyl group having from 6 to 18 carbon atoms.
59. A compound according to embodiment 56 which is 4-(3,5-di-isopropyl-4-hydroxyphenyl)-1,2-dithiole-3-thione.
60. A compound according to embodiment 56 which is 4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione.
61. A compound according to embodiment 56 which is 4-[3,5--bis(1,1-dimethylpropyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione.
62. A compound according to embodiment 56 which is 4-[3,5-bis(1,1-dimethylbutyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione.
63. A compound according to embodiment 56 which is 4-[3,5-bis(1,1,3,3-tetramethylbutyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione.
64. A compound according to embodiment 56 which is 4-[3,5--bis(1-methylcyclohexyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione.
65. A compound according to embodiment 56 which is 4-[3,5-bis(1,1-dimethylbenzyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione.

66. A compound according to embodiment 56 which is 4-(3-t-butyl-4-hydroxy-S-isopropylphenyl)-1,2-dithiole-3-thione.
67. A compound according to embodiment 56 which is 4-(3-t-butyl-4-hydroxy-5-methylphenyl)-1,2-dithiole-3-thione.
68. A compound according to embodiment 56 which is 4-[3-(1,1-dimethylpropyl)-4-hydroxy-5-isopropylphenyl]-1,2-dithiole-3-thione.
69. A compound according to embodiment 56 which is 4-[3-(1,1-dimethylbenzyl)-4-hydroxy-5-isopropylphenyl]-1,2-dithiole-3-thione.
70. A compound according to embodiment 56 which is 5-benzylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione.
71. A compound according to embodiment 56 which is 5-benzylthio-4-[3,5-bis(1,1-dimethylpropyl)-4-hydroxy-phenyl]-1,2-dithiole-3-thione.
72. A compound according to embodiment 56 which is 5-hexylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione.
73. A compound according to embodiment 56 which is 5-hexylthio-4-[3,5-bis(1,1-dimethylbutyl)-4-hydroxy-phenyl]-1,2-dithiole-3-thione.

74. A compound according to embodiment 56 which is 5--octadecylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione.

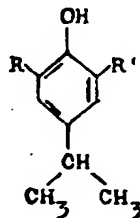
75. A compound according to embodiment 56 which is 5-octadecylthio-4-[3,5-bis(1,1-dimethylbenzyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione.

76. A compound according to embodiment 56 which is 5--allylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione.

77. A compound according to embodiment 56 which is 5--cyclohexylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione.

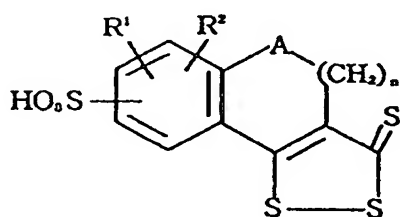
78. A compound according to embodiment 56 which is 4-(3,5-di-sec-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione.

79. A compound of embodiment 56 in which Y is hydrogen of the following formula



in which R and R1 have the meanings indicated in embodiment 56

80. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments comprising





wherein A is a methylene group or an oxygen atom; R' and R<sup>2</sup> are independently a hydrogen atom, a hydroxyl group, a halogen atom, a lower alkyl group or a lower alkoxy group; and n is an integer of 0-3 when A is a methylene group, and an integer of 1-3 when A is an oxygen atom; or a salt thereof.

81. A compound according to Embodiment 80 wherein A is a methylene group and R<sup>2</sup> is a hydrogen atom; or a salt thereof.

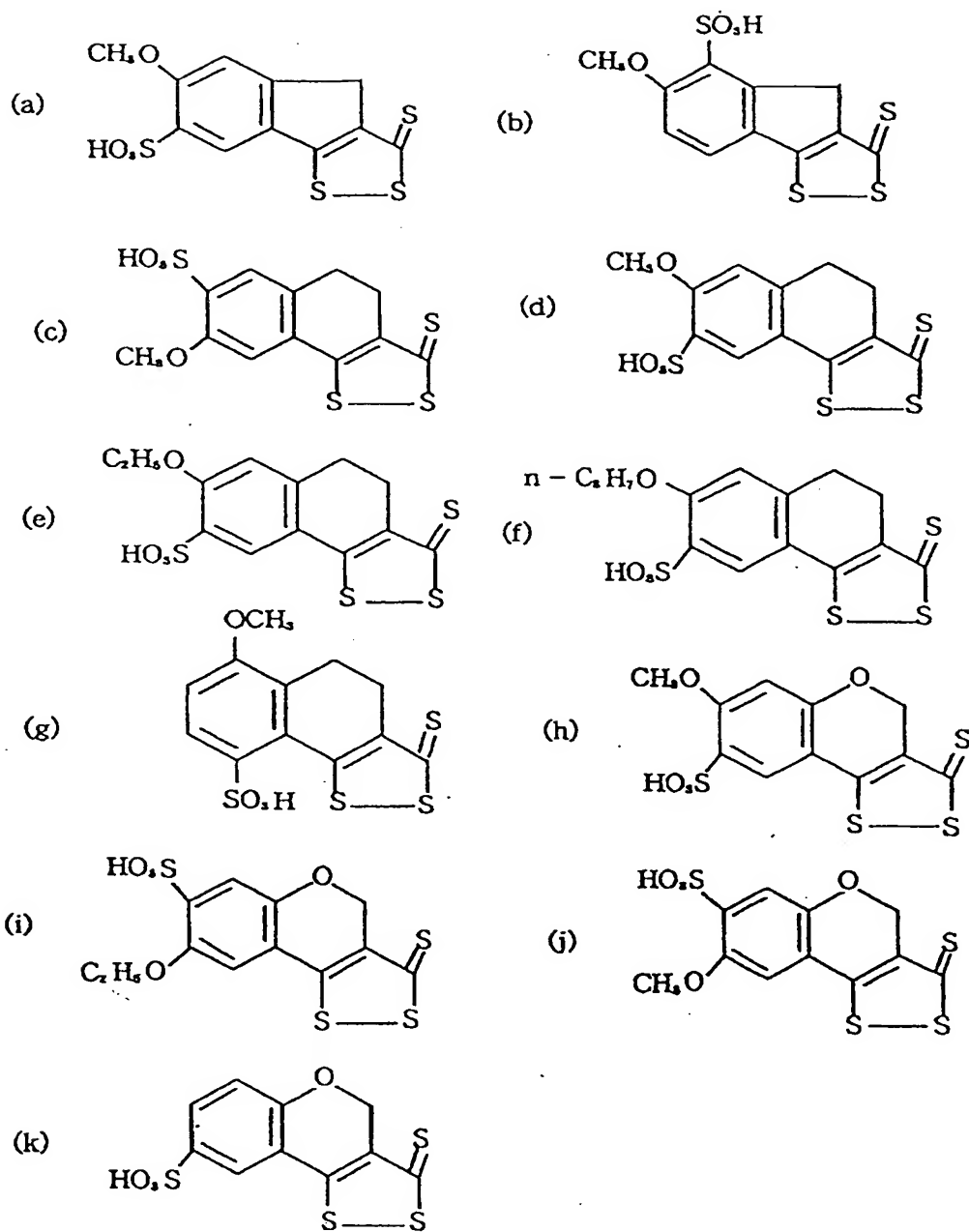
82. A compound according to Embodiment 81 wherein R' is a hydrogen atom, a hydroxyl group or a lower alkoxy group; or a salt thereof.

83. A compound according to Embodiment 82 wherein R' is a lower alkoxy group; or a salt thereof.

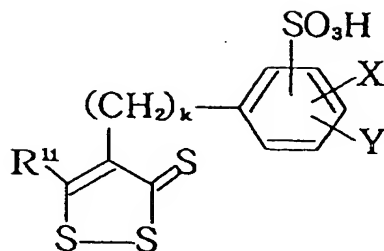
84. A compound according to Embodiment 82 wherein A is an oxygen atom and R<sup>2</sup> is a hydrogen atom; or a salt thereof.

85. A compound according to Embodiment 84 wherein R is a hydrogen atom, a hydroxyl group or a lower alkoxy group; or a salt thereof.

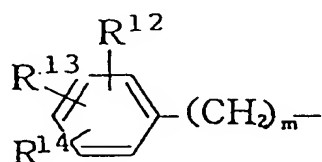
86. A compound according to Embodiment 80, which is any of the following compounds (a) to (k); or a salt thereof.



87. A compound represented by general formula



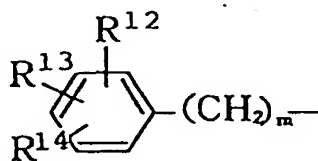
wherein k is an integer of 0-5; X and Y are independently a hydrogen atom, a lower alkyl group or a lower alkoxy group;  $R^{11}$  is an alkyl group or a group represented by general formula



(wherein m is an integer of 0-4; and  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  are independently a hydrogen atom, a lower alkyl group or a lower alkoxy group; however, a case is excluded in which both k and m are zero, the sulfonamide group bonds to the 3-position, X is a 4-methoxy group, and  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ , and Y are each a hydrogen atom); or a salt thereof.

88. A compound according to Embodiment 87 wherein  $R^{11}$  is an alkyl group; or a salt thereof.

89. A compound according to Embodiment 87 wherein  $R^{11}$  is a group represented by general formula



(wherein m, R12, R13 and R14 are the same as defined above and the sulfo group bonds to the 3-position, X is a 4-methoxy group, and R12, R13, R14 and Y are each a hydrogen atom); or a salt thereof.

91. A compound according to Embodiment 87, which is any of the following compounds; or a salt thereof 5-Hexyl-4-(4-methoxy-3-sulfobenzyl)-3H-1,2-dithiole-3-thione

4-(4-Methoxy-3-sulfophenyl)-5-(p-tolyl)-3H-1,2-dithiole-3-thione

92. A method for reducing the level of iron in the cells of living subjects by administering a pharmaceutical formulation comprising one or more of the compounds disclosed in embodiments 1 to 91

93. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and

Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments comprising one or more compound according to embodiments 1 to 91 wherein the compound is micronised.

94. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever; amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in

certain body compartments comprising one or more compound according to embodiments 1 to 91 wherein the compound is administered in an ophthalmic solution.

95. An ophthalmic solution according to embodiment 94 which also comprises an anti microbial preservative.
96. A compound according to embodiment 1 to 91 wherein the compound is administered to a mammal and functions as a chelating agent specifically for Iron and/or Copper.
97. A method for reducing the level of iron in the cells of living subjects by administering a pharmaceutical formulation comprising one or more of the compounds disclosed in embodiments 1 to 91 in combination with phosphatidyl-choline or Di-phosphatidyl-choline.
98. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis

hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments comprising one or more compound according to embodiments 1 to 91 wherein the compound is administered in combination with Phosphatidyl-choline or Di-phosphatidyl-choline.

99. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments comprising one or more compound according to embodiments 1 to 91 wherein the compound is complexed with Phosphatidyl-choline or Di-phosphatidyl-choline.

100. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments comprising one or more compound according to embodiments 1 to 91 wherein the compound is complexed with a Cyclodextrin.

101. A method for the treatment of; depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell



death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder , Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments comprising one or more compound according to embodiments 1 to 91 wherein the compound is administered as part of a combination therapy along with the compound Magnolol and/or its analogues and/or derivatives.

102. The use of D-amino acid oxidase inhibitors in the preparation of medicaments for the treatment of depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder , Major Depressive Episode including Chronic Type, Melancholia and

Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease, reducing iron levels in mammals, reducing transition element ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments.

103. D-amino acids oxidase inhibitors according to embodiment 102 which are identified as one or more compounds as listed in embodiments 1 to 91.

104. The administration of Inhibitors of the enzyme D-amino acid oxidase to mammals as prophylactic and therapeutic for the treatment of depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, treatment of amnesia, head injuries, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia and post stroke dementia, Down's syndrome, hereditary cerebral haemorrhage, amyloidosis of the Dutch type, Familial Mediterranean Fever, amyloid associated with type 11 diabetes, Creutzfeldt-Jakob disease, hypoxic damage, necrotic cell death, hypoxic damage, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis and carpal tunnel syndrome, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, Major Depression, Dysthymia, Depressive Disorder, Major Depressive Episode including Chronic Type, Melancholia and Seasonal Pattern. Bipolar Disorders, Cyclothymia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder, persons to effect future memory enhancement, aluminium overload, reperfusion injury, solid tumors (e.g. neuroblastoma), hematologic cancers, malaria, renal failure, liver disease,

reducing iron levels in mammals, reducing free transition metal ion levels in mammals, thalassemia, anemia, hereditary hemochromatosis hemodialysis, rheumatoid arthritis, patients having toxic amounts of metal in the body or in certain body compartments.

105. The administration of D-amino acid oxidase inhibitors according to embodiment 104 in combination with glutathione precursors or regenerations eg. N-acetylcystein, 2-oxo-thiazolidine-4 carboxylic acid, timonacic acid and WR-2721 (Walter Reed), diethyldithiocarbamate disulfiram (ANTABUSE) Malotilate (Kantec), Sulfarlem and Oltipraz.

106. Inhibitors according to embodiments 102,103,104 and 105 which include:

2-oxo-3-pentynoate

Acetylacetone

Kojic Acid.

107. An assay to determine Oxidative Stress which will determine if a mammal has a neurological disorder or the propensity of a mammal to develop such a disorder.

The oxidation of D-amino acids should be balanced by antioxidant mechanisms to keep ammonia and hydrogen peroxide levels in control. A blood assay is outlined which can determine the oxidative stress index of the Patent.

A blood sample approx. 5mls is taken from the mammal the RBC's are separated and the serum used to determine the level of  $H_2O_2$  (hydrogen Peroxide present) and another aliquot of the same sample is treated with a small quantity of D-amino acids (all 20 AA) and incubated for a short while and the  $H_2O_2$  hydrogen Peroxide level present measured. A normal young mammal will be able to balance the generation of  $H_2O_2$  and  $NH_4^+$  by the DAAO enzyme with generated glutathione for of the  $H_2O_2$  together with catalase enzyme

and the production of glutamate and neutralization of glutamine for the removal of the  $\text{NH}_4^+$ . However in aged mammals and others (Alzheimer's patients) with oxidative stress imbalances  $\text{H}_2\text{O}_2$  and Ammonia will increase in concentration and will slow this in the blood assay demonstrating their ability to contain their DAAO activity.

107. An assay to determine oxidative stress which will determine if a mammal has a neurological disorder or the propensity of a mammal to develop such a disorder wherein the test determines the ammonia and/or hydrogen peroxide produced in a blood/serum sample of the mammal which is challenged with one or more D-amino acids.
108. An assay according to embodiment 106 and/or 107 wherein the DAAO action is monitored by PCR activity of the differing enzyme systems of the anti-oxidative system.
109. A method of assaying for probable Alzheimer's disease in a human which comprises determining in a sample of human circulatory fluid the amount of  $\text{H}_2\text{O}_2$  present in the sample after said sample has been treated with a D-amino acid.
110. A method of assaying for probable Alzheimer's disease in a human which comprises determining in a sample of human circulatory fluid the amount of ammonia present in the sample after said sample has been treated with a D-amino acid.
111. The method according to claim 108 and 109 wherein the circulatory fluid is blood plasma and/or spinal fluid.
112. A method of assaying for probable Alzheimer's disease in a human which comprises determining in a sample of human cerebrum material the amount of ammonia present in the sample after said sample has been treated with a D-amino acid.
113. A pharmaceutical agent comprising one or more of the compounds according to embodiments 1 to 91 inclusive for the treatment of cerebropathy.

114.A pharmaceutical agent comprising one or more of the compounds according to embodiments 1 to 91 inclusive for the treatment of neurospanchnic disorders.

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